"Advancements in the Synthesis and Biological Applications of 1,2,4-Triazoles: A Review"

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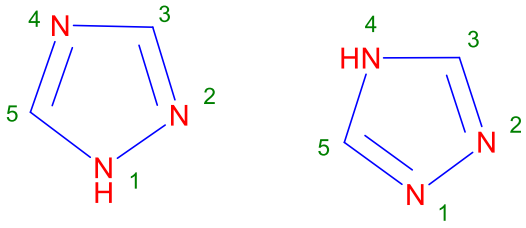
Introduction:

Triazole is a five-membered heterocycle with three nitrogen atoms at 1, 2, and 1, 4 positions. Bladin was the first scientist to give the name "triazole" to the carbon nitrogen ring system. ($C_2N_3H_3$) and described triazoles' derivatives (Singh, & Kandel, 2012). In recent decades, the chemistry of 1, 2, 4-triazoles and their fused heterocyclic derivatives has attracted significant attention due to their synthetic and biological relevance (Miyauchi, et al. 1995).

1,2,4-triazoles are formed by precisely arranging three nitrogen atoms and two carbon atoms, resulting in unusual features such as weak contacts, basicity, and many coordination modes (Zhang, 2014, Holm, 2011, Kingele, 2003, Strzelecka & Swiatek, 2018). 1,2,4-triazoles exist in two isomeric forms: 1H-1, 2, 4-triazole and 4H-1,2,4-triazole (Chawla et al. 2013). Several investigations suggest that tautomer is more stable than tautomer (Pinto et al. 2007).



1H-1,2,4-Triazole 4H-1,2,4-Triazole

Fig. 1: Isomeric forms of 1,2,4-Triazole

Physical Properties:

1,2,4-Triazoles demonstrates the following physical properties:

1. Chemical formula: $C_2H_3N_3$ and molar mass per mole: 69.07 g/mol.
2. The solid 1,2,4-triazole is white in colour.
3. It has a melting point of 119-121˚C and boiling point of 260˚C.
4. At 25˚C, it has a density of 1.13 g/cm^3.
5. 1,2,4-triazole is basicin nature and has strong stability for thermal and acidic

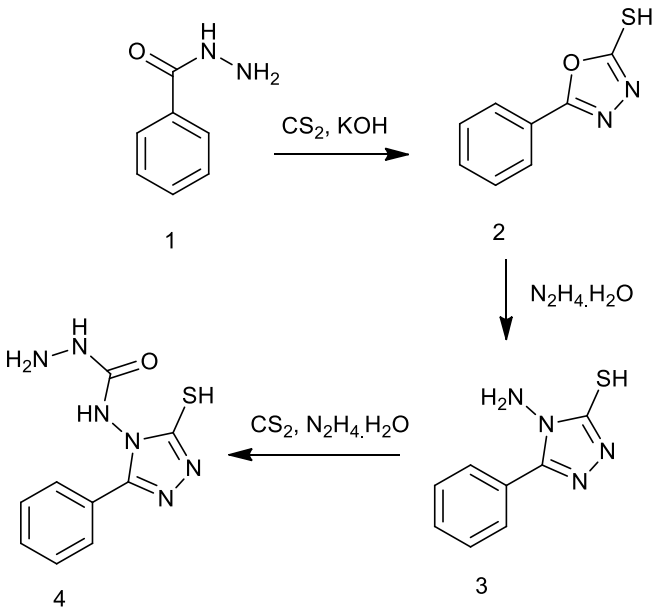
conditions.

1,2,4-triazole is highly soluble in water. It is also soluble in most organic solvents such as alcohol, propanol, isopropanol, methyl acetate, and ethyl acetate (National Center for Biotechnology Information, 2024, Motornov et al., 2018).

Synthesis of 1,2,4-Triazoles:

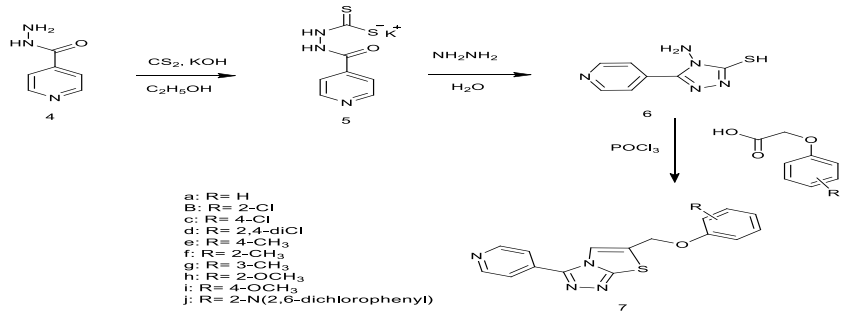
1. From Carboxylic Acid Hydrazide:

N-(3-mercapto-5-phenyl-4H-1,2,4-triazol-4-yl) hydrazine carbothioamide **(4)** is made by combining 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol and thiosemi-carbozide (III), which is created through hydrazine hydrate reaction and 5-phenyl-1,3,4-oxadiazol-2-ylamine (II), which was produced from benzoic acid hydrazide (I) (Aday, 2013), as illustrated in **Scheme 1**. While 6-(substituted)-3-(pyridin-4-yl)-1,2,4-triazole [3,4-b].



Scheme 1: Synthesis of N-(3-mercapto-5-phenyl-4H-1,2,4-triazol-4-yl) hydrazine carbothioamide

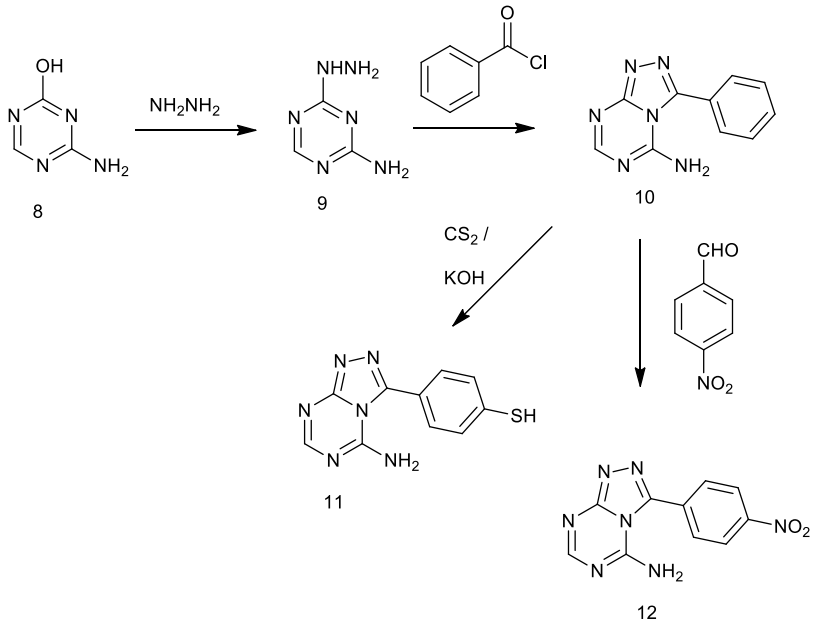
6-(substituted)-3-(pyridin-4-yl)-1,2,4-triazole [3,4-b] [1,3,4] thiadiazole **(7)** synthesizes isonicotinic acid hydrazide (I), which is then transformed to potassium dithiocarbazinate (II). The salt (II) was treated with hydrazine hydrate to produce 1,2,4-triazole (III), which was then treated with carboxylic acids to produce a sequence of compounds **(7a-j)** (Ramesh et al., 2013), as illustrated in **Scheme 2.**



Scheme 2: Synthesis of 6-(substituted)-3-(pyridin-4-yl)- 1,2,4-triazole[3,4-b][1,3,4]thiadiazole

2. From 1, 3, 5-Triazine:

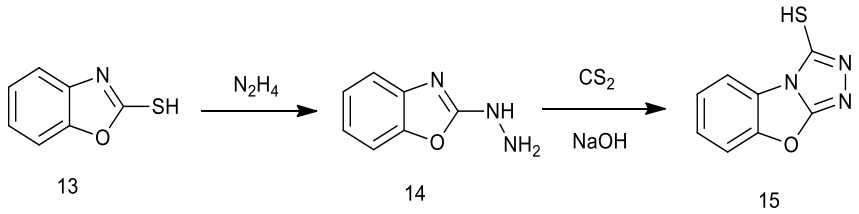
5-amino-3-(p-nitrophenyl) [1,2,4] triazolo[4,3-a] [1,3,5] triazine **(12)**, 5-amino[1,2,4]triazolo[4,3-a].[1,3,5]triazine-3-thiol **(11)** and 5-amino-3-phenyl[1,2,4]triazolo[4,3-a][1,3,5]triazine **(10)** were synthesized from 2-amino-4-hydrazino-1,3,5-triazine (II), which was prepared by substituting the hydroxy group with a hydrazino group (Salih & Ibraheem, 2008), as shown in **Scheme 3.**



Scheme 3: Synthesis of 1,2,4-triazole derivates from 1,3,5- triazine

3. From Oxazole:

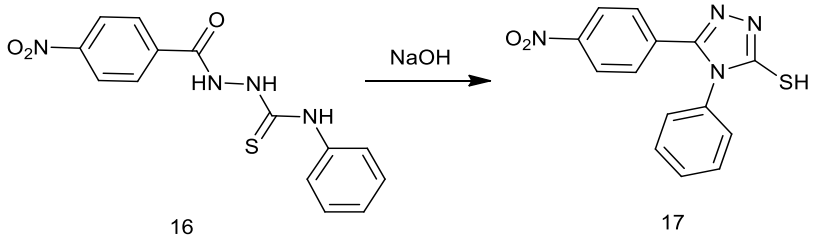
Substituting the mecapto group in 2-meracpto benzoxazole **(13)** with hydrazino group yields 2-hydrazino benzoxazole **(14).** Reacting **(14)** with carbon disulfide and sodium hydroxide yields 1,2,4-triazole [4,3-b] benzoxazole-1-(2H)thione **(15)** (Askar et al., 2013), as indicated in **Scheme 4.**



Scheme 4: Synthesis of 1,2,4-triazole [4,3-b] benzoxazole- 1-(2H)thione

4. From Thiosemicarbazide:

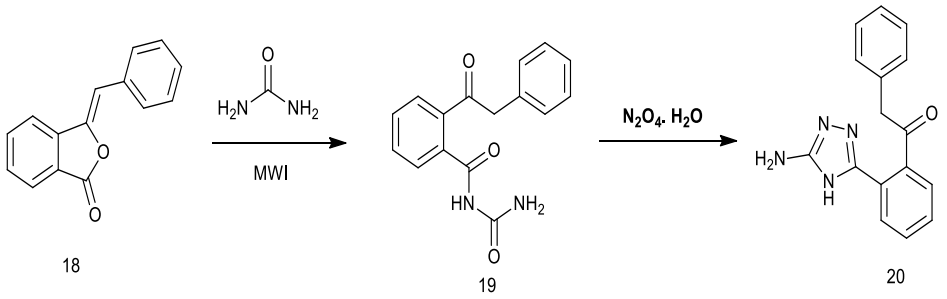
Scheme 5 illustrates the preparation of 5-(4-Nitrophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol **(17)** from 1-phenyl-4-(4-nitrobenzoyl)thiosemicarbazide **(16)** (Hashim, & Alias, 2012).



Scheme 5: Synthesis of 5-(4-Nitrophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol

5. From Urea:

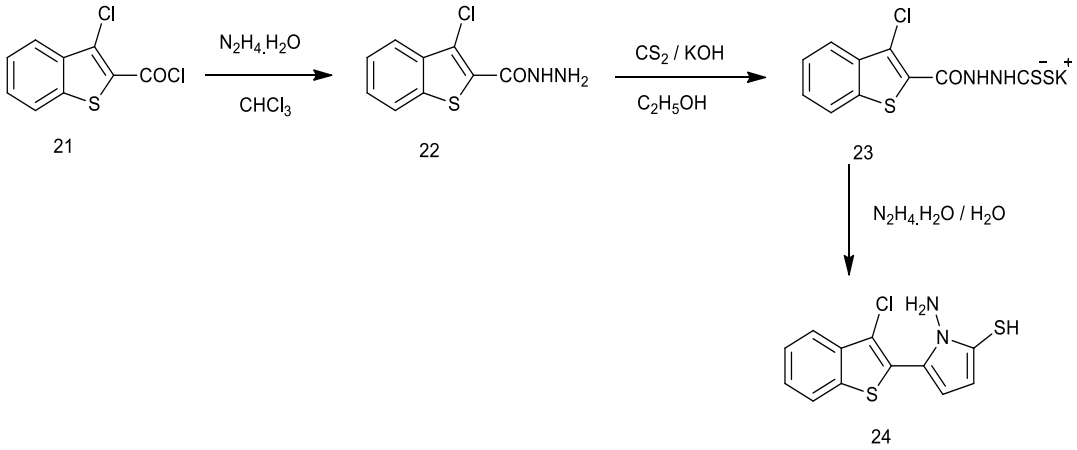
Under microwave irradiation (MWI), 3-benzylidene phthalide (I) reacts with urea to produce 1-(2-(α-phenylacetyl)benzoyl)urea (II), which then reacts with hydrazine hydrate to produce 1-(2-(5-amino-4H-1,2,4-triazol-3-yl)phenyl)-(2-phenylethanone) (III) (Younis, 2011), as indicated in **Scheme 6.**



Scheme 6: Synthesis of 1-(2-(5-amino-4H-1,2,4-triazol-3- yl)phenyl)-2-phenylethanone

6. From Acid Chloride:

Heating 3-chloro-2-chlorocarbonylbenzo[b]thiophene **(21)** with hydrazine hydrate produced its equivalent hydrazide **(22).** Potassium dithiocarbazate **(23)** was cyclized with hydrazine to produce 4-amino-5-(3-chlorobenzo [b] thien-2-yl).-3-mercapto-1,2,4-triazole **(24)** (Ashry et al., 2006), as illustrated in **Scheme 7.**



Scheme 7: Synthesis of 4-amino-5-(3-chlorobenzo[*b*]thien- 2-yl)-3-mercapto-1,2,4-triazole

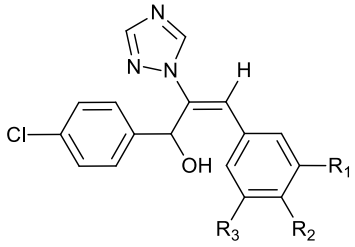
Biological Applications:

1. 1,2,4-Triazoles as Antibacterial Agents:

Various antibiotics have been developed to combat bacterial infections. Overuse of antibiotics has led to the development of antibiotic-resistant microorganisms, potentially posing a worldwide threat. A health disaster. It is advised that you use new antimicrobial

agents having higher broad-spectrum potency. As a result, current efforts have focused on researching innovative antibacterial agents. Antibacterial drugs are chemicals derived by a mold or bacterium capable of killing microorganisms and treat bacterial illnesses. (Singh, 2011).

Uchil et al. (2002) developed and utilized substituted-(+)α-(4-chlorophenyl)-β-(phenylmethylene)-1H-1,2,4-triazole-1-ethanols **(25)** as a bacteriostatic agent. (Figure 2)



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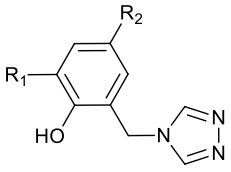
a: R_1=R_3=H; R_2=Cl
b: R_1= Br; R_2=R_3=H
CR_1=R_2=R_3=OCH_3
d: R_1=OC_6H_5; R_2=R_3=H
c: R_1=R_3=H; R_2=SCH_3
f: R_1=OCH_3; R_2=OH; R_3=H
g: R_1=R_3=H; R_2=OH
h: R_1=R_2=OCH_2O; R_3=H
i: R_1=R_3=H; R_2=$N(CH_3)_2$

Figure 2: Substituted-(+)α-(4-chlorophenyl)-β-(phenylmethylene)-1H-1,2,4-triazole-1-ethanols as antibacterial agents

El-Zemity et al. (2006) synthesized and tested the Bactericidal Potential of (1H-1,2,4-triazol-1-yl) N,N-dialkyl Anilines **(26),** and N-alkyl Anilines **(27)**. (Figure 3)



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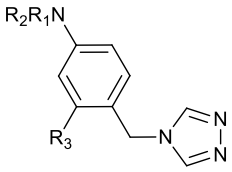

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a: R_1=R_2=H
b: R_1=CH_3; R_2=H
c: R_1=H; R_2=CH_3
d: R_1= i-C_4H_9; R_2=H
e: R_1=t-C_4H_9; R_2=CH_3
f: R_1=s-C_4H_9; R_2=CH_3

a: R_1=R_2=R_3=H
b: R_1=CH_3; R_2=R_3=H
c: R_1=C_2H_5; R_2=H; R_3=CH_3
d: R_1=C_2H_5; R_2=R_3=H
e: R_1=R_2=CH_3; R_3=h
f: R_1=R_2=R_3=CH_3

Figure 3: (1H-1,2,4-triazol-1-yl) N,N-dialkyl Anilines and N-alkyl Anilines as antibacterial agents

Narayana Rao et al. (2014) synthesized and analyzed a novel 1,2,4-triazole derivative. They also assessed the biological activity of 4-[(3-(4-substituted-phenoxymethyl)-5-

benzylsulfonyl)-1,2,4-triazol-4-yl] methyl].-morpholine **(28)** and all of the title compounds demonstrated good antibacterial properties. (Figure 4)

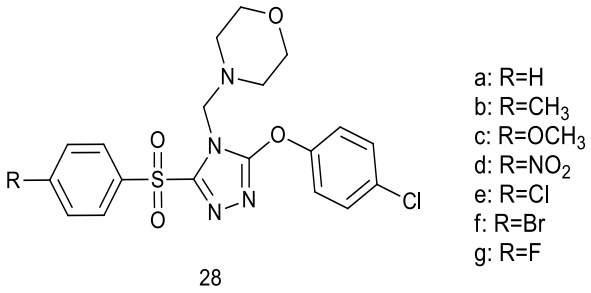

Figure 4: 4-[(3-(4-substituted-phenoxymethyl)-5-benzylsulfonyl)-1,2,4-triazol-4-yl] methyl].-morpholine as antibacterial agents

Besides these, Nitrofuryltriazoles **(29)** have promise for antibacterial action in the urinary tract (Akerblom et al. 1973). (Figure 5)

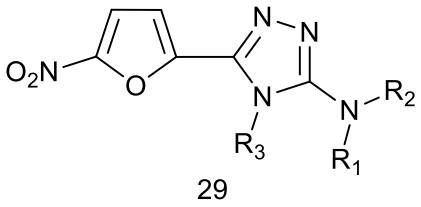

Figure 5: Nitrofuryltriazoles as antibacterial agents in urinary tract infections

2. 1,2,4-Triazoles as Antifungal Agents:

Antifungal medications treat and remove fungal infections in the body. They work by exploiting differences between mammalian and fungal cells to eliminate fungal organism without harming the host cells. As both the cells are eukaryotic in nature, so it is more difficult to design the drugs of antifungal activity with fine selections of the cells without causing any side effects (Tian et al. 2012).

1,2,4-triazole compounds have significant antifungal activity (A. Varvaresou 2000). Examples of antifungal medicines include fluconazole **(30) (**Tsukuda, 1998 & Arndt, 1988). itraconazole **(31)** (Mbailey, 1990), ravuconazole **(32)** (Roberts, 2000), voriconazole **(33)** (Espinel-Ingroff, 1998, J. A. Sabo & S. M. Abdel-Rahman, 2000), and posaconazole

(34) (Johnson & Kauffman, 2003). (Figure 6)

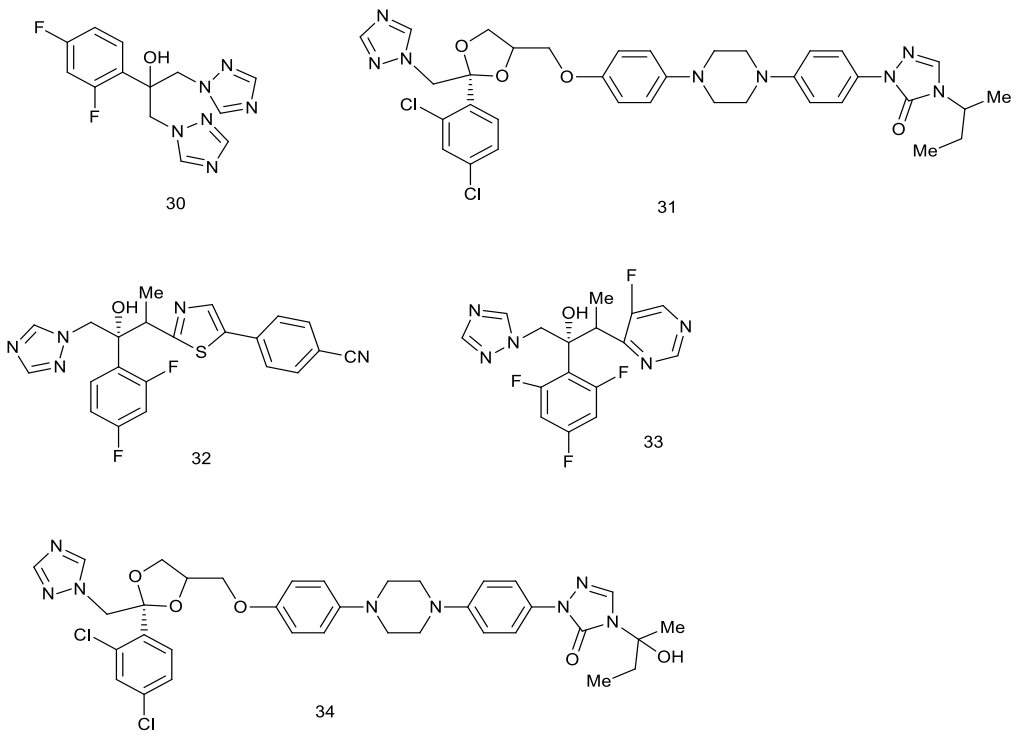

Figure 6: Antifungal drugs of 1,2,4-Triazoles

3. 1,2,4-Triazoles as Antitumor Agents:

Cancer, characterized by aberrant cell growth, is a significant global issue (Ferlay el al. 2013). Thus, the discovery and development of new effective and selective anticancer medications is critical in modern cancer research. Research on 1,2,4-triazole compounds has yielded promising findings (Chawla et al. 2013 & Murtaza et al. 2014). Li et al. (2012) synthesized and tested the anticancer efficacy of some hybrid 1,2,4-triazole Schiff's bases **(35)** with γ-substituted butenolide moiety (Li et al. 2012). (Figure 7)

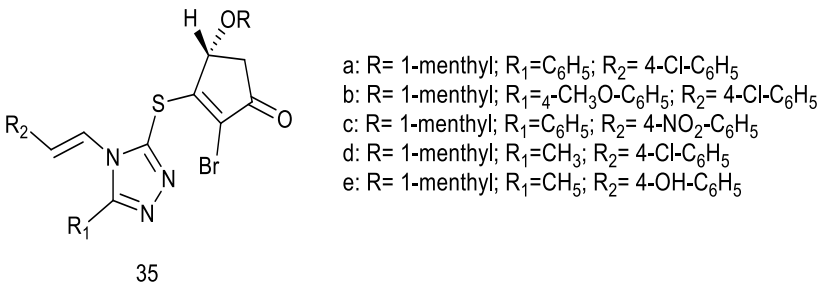

Figure 7: Substituted Schiff bases in the treatment of cancer

Anton Smith et al. (2014) produced and tested the in vitro anticancer activity of 1,2,4-

triazole derivatives **(36)**. (Figure 8)

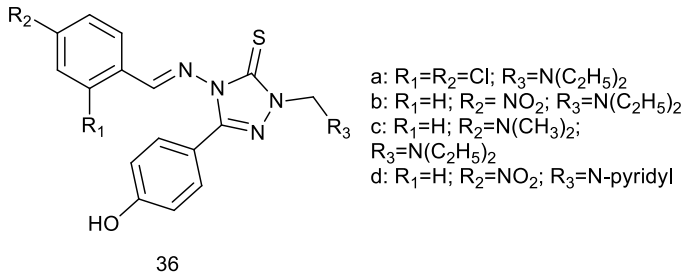

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Figure 8: Antitumor activity of substituted 1,2,4-Triazole derivatives

Baviskar et al. (2012) produced clubbed triazolyl indeno [1,2-C] isoquinolines **(37)** as an anticancer agent. (Figure 9)

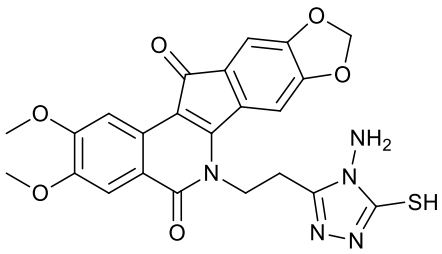

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Figure 9: Clubbed triazolyl indeno [1,2-C] isoquinolines as anticancer agent.

4. 1,2,4-Triazoles as Anti-inflammatory Agents:

The therapeutic use of nonsteroidal anti-inflammatory medicines (NSAIDs), which are used to treat a variety of arthritic disorders, is limited due to adverse effects such as gastrointestinal haemorrhage and ulceration. So, novel medicines with effective anti-inflammatory activity and little adverse effects have been created (Akhter et al. 2014).

Jiang et al. (2012) synthesized a series of hybrids from diaryl-1,2,4-triazole and N-hydroxyurea **(38)** and assessed their anti-inflammatory efficacy in acetic acid-induced writhing and hot-plate assays. They found potential analgesic action. (Figure 10)

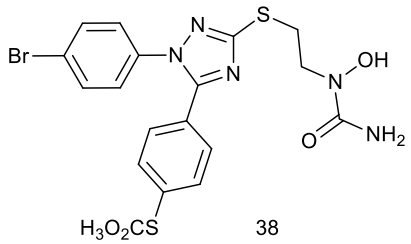

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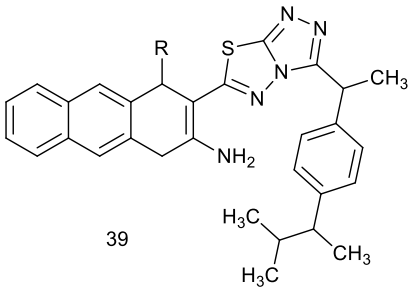
Figure 10: Diaryl-1,2,4-triazole and N-hydroxyurea as anti-inflammatory agents

Subbarao et al. (2014) have been evaluated a good anti-inflammatory activity of novel series of 1,2,4-triazolo [3,4- b] [1,3,4] thiadiazoles **(39)**. (Figure 11)



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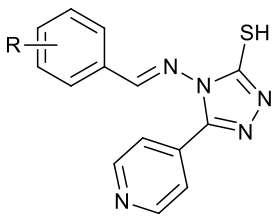
R=C_6H_5; 2-Cl-C_6H_4; 4-OH-C_6H_4; 2-OMe-C_6H_4;
4-OMe-C_6H_4; 2-NO_2; 4-NO_2-C_6H_4;
2-Thiophenyl; Pyridinyl; 3-Indolyl

Figure 11: Novel series of 1,2,4-triazolo [3,4- b] [1,3,4] thiadiazoles as anti-inflammatory agents

Murti et al. (2011) have been characterized the anti-inflammatory activity of 4-(Substituted benzylideneamino)-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-thiol derivatives **(40)**. (Figure 12)



40

R=4-Cl; 3-OH;
4-OMe; 2-NO_2;
4-$N(CH_3)_2$

Figure 12: 4-(Substituted benzylideneamino)-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-thiol derivatives as anti-inflammatory agents

5. 1,2,4-Triazoles as Anticonvulsant Agents:

Anticonvulsants are medications that prevent or reduce the severity and frequency of seizures in various forms of epilepsy. Anticonvulsants can operate on different brain

receptors and have varying effects (Chornicle et al. 2004).

Alprazoam and other 1,2,4-triazole compounds are regarded effective anticonvulsants. Wingrove et al. proposed that the activity of loreclezole **(41)**, a second-generation antiepileptic medication, depends on the interaction between the triazole moiety and the amide group of asparagine (Asn-289), which is situated on the β2 subunit of the GABAA receptor (Wingrove et al. 1999). (Figure 13)

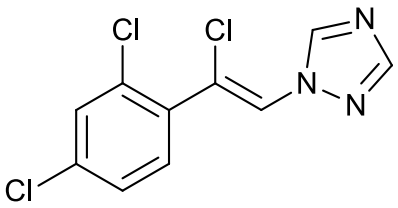


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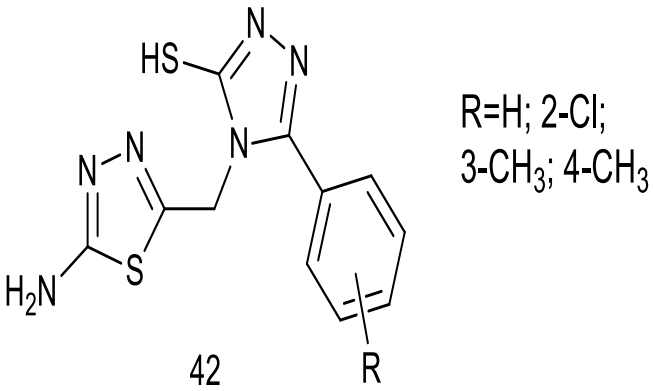
Figure 13: Anticonvulsant drug Loreclezole

D. Kumudha et al. examined the anticonvulsant and CNS depressive activities of 1,3,4-thiadiazoles with substituted 1,2,4-triazole moiety **(42)** (Singh & Chouhan, 2014). (Figure



42 R

14)

Figure 14: Anticonvulsant and CNS depressive activity of 1,3,4-thiadiazoles with substituted 1,2,4-triazole

Abbreviations (Solvents and Reagents)

CS_2	Carbon disulfide
C_2H_5OH	Ethyl alcohol
KOH	Potassium hydroxide
N_2H_4	Hydrazine hydrate
$POCL_3$	Phosphoryl chloride
CH_3	Methyl

C_2H_5	Ethyl
OCH_3	Methoxy
NaOH	Sodium hydroxide
$CHCl_3$	Chloroform
NO_2	Nitro
MWI	Microwave irradiation
NSAIDs	Nonsteroidal anti-inflammatory medicines
Asn	Asparagine
GABAA	γ-aminobutyric acid
CNS	Central nervous system

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